REMARKS:

Please amend claims 1, 2, 6, 8 and 14 as indicated.

The amendments to claims 1, 2, 6, 8 and 14 are fully supported by the specification. The amendments to claim 1 are supported by originally-presented claim 2 as well as by page 3, lines 4-5 and page 6, lines 22-23. The amendments to claim 8 are likewise supported by page 3, lines 4-5 and page 6, lines 22-23, as well as originally-presented claim 14. The amendments to claims 2 and 6 perfect the antecedent basis of recited terms. The amendment to claim 15 corrects the claim dependency.

The amendments to the specification merely correct the spelling and therefore are not new matter.

Applicant appreciates the Examiner's review and consideration of the information disclosure statement filed February 19, 2004.

Rejections under 35 U.S.C. 112, first and second paragraphs

Claims 1, 6-13 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for functionalized hyaluronic acids with the crosslinker of a dihydrazide of the formula of claims 2 and 14, does not reasonably provide enablement for other types of derivatives of functionalized hyaluronic acids.

Applicant respectfully disagrees.

The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. Esterification of the carboxyl group of the glucuronic acid moiety of hyaluronan is known in the art and is fully enabled (see for instance the references cited

on page 2, line 20-page 3, line 2). Furthermore, the specification provides relevant teaching enabling esterification. See for instance p. 11, lines 2-4. It is also noted that the Examiner has cited as 102(b) art both USP 5,690,954 and Kyyrönen et al, both of which teach esterification of the carboxylic acid groups in hyaluronan; the Examiner's recitation of these references inherently support that hyaluronic acid esters are enabled. Nevertheless, Applicant has amended claim 1 to recite only dihydrazide crosslinkers having the formula H_2N-NH-CO-A-CO-NH-NH_2. Consequently, Applicant believes this rejection has been obviated.

Claims 1, 6-10 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Applicant respectfully disagrees.

The Examiner asserts that there is insufficient description support provided in the specification for the following terms: "hyaluronan functionalized", "functionalized hyaluronic acid" and "derivitized hyaluronan". On the contrary, the specification recites numerous instances of these terms and make clear what they mean. The specification teaches that "a large number of sodium hyaluronate derivatives have been synthesized by esterification of the carboxyl group of the D-glucuronic acid moiety of the sodium hyaluronate" (page 2, lines 20-21) and that "sodium hyaluronate can also be derivitized by covalent attachment of hydrazides at carboxyl groups of glucuronic acid moieties (page 3, lines 4-5). These recitations make clear that the meaning of "derivitized hyaluronan" is hyaluronan which has been chemically reacted such that there is a covalent attachment of another molecule to the hyaluronan. In the instant invention, the

hyaluronan is reacted with a dihydrazide to form the derivitized hyaluronan which has a pendant hydrazido group (page 16, lines 19-20) The specification further teaches that "the hyaluronate is functionalized by covalent attachment of homobifunctional crosslinking groups" and "is preferably functionalized at carboxyl group of glucuronic acid moieties" (page 10, lines 4-7) These recitations make clear that the terms "hyaluronan functionalized" and "functionalized hyaluronic acid" refer to hyaluronan which has had attached to it a molecule with one or more functional groups. See also page 10, line 29- page 11, line 1.

Furthermore, the term "functionalized hyaluronic acid", "hyaluronan functionalized" and "derivitized hyaluronan" are terms in the prior art. See for instance USP 5,616,568, column 2, line 9-12, 35 and 39; column 3, lines 39-40, 44, 52 and 57; column 13, lines 7 and 56; and claim 1.

The structure of hyaluronan is clearly described in the instant specification (page 2, lines 6-7 and page 7, lines 9-11). The general structure of the glucuronic acid carboxyl group of hyaluronan functionalized with a dihydrazide is shown schematically on page 10, lines 4-27. One amine group of the dihydrazide reacts with a carboxyl group of a glucuronic acid moiety, forming a peptide bond. The other amine group of the dihydrazide is thus covalently attached to the hyaluronan. In other words, the hyaluronan is functionalized with the free amine group. As the specification teaches, this free amine group can react with other groups to form crosslinks, either within the same functionalized hyaluronan (intramolecular crosslink) or with a second molecule (intermolecular crosslink) which can be hyaluronan or another material, e.g. a therapeutic (page 15, lines 3-6).

Applicant therefore believes the specification provides sufficient written description for the terms and structures recited therein.

Claims 1, 4 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant believes the amendments to the claims overcome each of these rejections.

Claim 1 has been amended to provide antecedent basis for the term "the derivitized hyaluronan".

Claim 1 has also been amended to recite "carboxyl groups of glucuronic acid sites" thereby providing antecedent basis for the phrase in claim 4.

The amendment to claim 8 provides antecedent basis for the term "wherein A is" recited in claim 15.

Rejections under 35 U.S.C. 102(b) and 103(a)

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Illum of USP 5,690,954.

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kyyrönen et al.

Claim 6 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Illum of USP 5,690,954.

Claim 6 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kyyrönen et al.

The amended claims are drawn to microspheres comprising hyaluronan derivatized with a crosslinker at carboxyl groups of glucuronic acid sites of the hyaluronan, wherein the crosslinker is a dihydrazide having the formula: H_2N-NH-CO-A-CO-NH-NH_2. USP 5,690,954 teaches microspheres made of "hyoluronic acid esters" (column 6, line 13-20). Kyyrönen et al teach films and microspheres prepared from various esters of hyaluronic acid (see entire document). Neither reference teaches or suggests derivatizing hyaluronic acid with any dihydrazide or making microspheres of hyaluronic acid derivatized with a dihydrazide. Indeed, each reference is silent on hyaluronan functionalized with dihydrazides. Therefore, the amended claims are not anticipated by either reference.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouyani et al of USP 5,616,568 in view of Kyyrönen et al.

USP 5,616,568 ('568) teaches the functionalization of hyaluronic acid with dihydrazides for the production of hyaluronic gels or hydrogels. As conceded by the Examiner in his rejection, USP 5,616,568 is entirely silent on using hyaluronic acid functionalized with dihydrazide for the production of microspheres. Indeed, the teachings in '568 cited by the Examiner teach away from such production. The Examiner notes that the reference states that functionalized hyaluronic acid compositions can be thought of as being composed of hydrophilic monomer units linked to form a soluble

polymeric network and eventually crosslinked to form an insoluble network (column 3, lines 44-51). This statement comes at the end of the following paragraph:

> The functionalized HA compositions of the invention form biocompatible gels or hydrogels. The term gel is intended to mean viscous or semi-solid and jelly-like. The term hydrogels is intended to mean macromolecular networks that swell in water. They can be thought of as being composed of hydrophilic monomer units linked to form a soluble polymeric network and eventually crosslinked to form an insoluble network. (column 3, lines 44-51)

The hydrogels of '568 are additionally described as "pore-containing matrices" (column 13, line 58) and "an ordered macroporous structure" (column 33, line 35). Indeed, some of the hydrogels were examined using scanning electron microscopy and found to have pores ranging from 20-100 μm in one instance and 20-50 μm in another (column 33, Example 8). Gels, hydrogels and insoluble networks are diametrically opposite to microspheres. Microspheres are particulate. As taught in the instant invention, microspheres are substantially spherical particles with a diameter in the about 1 to about 500 μm range (page 2, lines 2-3 and page 8, lines 8-9) which are globules (page 15, line 2). Such spherical particles are not *macroporous* structures. A spherical particle has a finite and roughly identical size in each of three dimensions, while a matrix or gel or ordered macroporous structure may have different sizes in each dimension. The microspheres of the instant invention can advantageously *encapsulate* pharmacological and cosmetic agents (page 1, lines 17-20 and page 15, line 21-page 16, line 11). While the hydrogels of '568 are carriers of agents (column 13, line 7-10), they cannot encapsulate agents in individual units as can microspheres.

Kyyrönen et al teach films and microspheres prepared from various esters of hyaluronic acid. Notably, Kyyrönen et al is entirely silent on hyaluronic acid

functionalized with hydrazides and thus does not teach or suggest microspheres made from hydrazide-functionalized hyaluronan.

It is also noted that the hydrogels of '568 find use in tissue engineering where the defined pores can support cells such as keratinocytes, chondrocytes and osteoblasts to adhere and grow within the hydrogel for use in skin grafts, nerve repair and cartilage and bone repair (column 14, lines 16-29). Indeed, the pore sizes of the hydrogels are the same order of magnitude as the diameters of the microspheres, suggesting that the structure of microspheres is inappropriate for their use in supporting cell growth. Trying to combine the teachings of Kyyrönen et al with those of '568 to yield microspheres would in fact defeat the purpose and use of the hydrogels of '568.

As such, there is no suggestion or motivation in either of these two references for one of ordinary skill in the art to combine these two references to arrive at the instant invention. Furthermore, the Examiner has not supplied evidence of suggestion or motivation to combine these two references in the knowledge generally available to one of ordinary skill in the art at the time the instant invention was made. In addition, the teachings of '568 regarding gels and hydrogels as insoluble networks teach away from microspheres. Furthermore, if one attempted to combine the teachings of '568 with those of Kyyrönen et al to produce the instant inventive microspheres, it would defeat the purpose of the invention taught in the '568 patent.

Accordingly, Applicant requests the withdrawal of this rejection.

Review and reconsideration are respectfully requested.

Respectfully submitted,

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